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(54) Title: PHARMACOLOGICAL COMPOSITIONS CONTAINING EXTRACTS DERIVED FROM GRAMINEAE PLANT FAMILY AND USES THEREOF

(57) Abstract

A pharmacologically effective composition for direct introduction into body tissues or vessels for treatment thereof or for treatment of proximate or remote tissues or for systemic effects. The composition includes a carrier and a sterile refined extract derived from Gramineae, particularly cereal plants. Green components of the plants yield a juice which is refined to comprise liquid fractions only from the juice. The composition is used for the manufacture of a medicament for use in the treatment of pathological conditions including tumours and viral infections, for analgesic effects, and treatment of lesions.

PHARMACOLOGICAL COMPOSITIONS CONTAINING EXTRACTS DERIVED FROM GRAMINEAE PLANT FAMILY AND USES THEREOF

This invention relates to pharmacologically effective compositions and their uses for human or veterinary treatment.

In patent specification No. AU 81,985/87 there is described a pharmacological or cosmetic substance for external application. The product or substance includes an extract from plants of the grass family of plants, the extract including juice freshly derived from the green components of the plants and stabilised within two hours of derivation from the plants. The stabilisation consists of stabilisation by a process selected from: (1) the process of concentrating the derived juice to provide a concentrated liquid, (2) the process of spray drying of the derived juice, (3) the process of freeze drying of the derived juice, and (4) the process of blending the derived juice with a preserving agent. The extract is carried in a pharmaceutically acceptable base carrier or excipient, the carrier preserving the extract against deterioration and being capable of at least partial absorption by tissues so as to carry the extract to sub-surface tissues.

This composition or product has been found to be useful for external topical application for the treatment of skin or mucous tissue infections, lesions, injuries and the like. However, the substance has been limited to external application and the rate of effective action of the substance can be limited by the rate at which the active components are taken up into the tissues being treated.

In Patent Specification No. GB 1358052 there is described a powder which is a spray dried or lyophilised juice of cereal plant leaves. The powder is described in detail for consumption as a food or beverage ingredient. However there is no suggestion of pharmacological use except a general reference to application to the skin as a medicine or cosmetic.

It is an object of the present invention to provide an effective pharmacological composition capable of rapid and/or dispersed activity in a patient or animal undergoing treatment. It is a further object to provide a process of preparing such a pharmacologically effective composition.

It is a further object to pr vide novel uses of a pharmac logically effective composition in the manufacture of medicaments for treatment of pathological conditions or for achieving other beneficial effects.

It is a further object to provide a novel method of treating a pathological condition or of achieving other beneficial effects in an animal.

According to the present invention there is provided a pharmacologically effective composition for treatment of responsive pathological conditions by direct introduction into body tissues or vessels for treatment thereof or for treatment of proximate or remote tissues or for systemic effects, the composition including biologically active agents from a refined extract derived from cereal plants or other plants of the Gramineae family, green components of the plants being processed to yield a juice and the juice being refined so as to eliminate all solid components and to provide the refined extract which comprises liquid fractions only from the juice, the refined extract being sterile, the composition further including a pharmacologically acceptable liquid carrier in which the biologically active agents from the refined extract are carried for direct introduction into the body tissues or vessels.

The biologically active agents from the refined extract are preferably included in the composition by mixing of the refined extract itself with the carrier to introduce those agents into the carrier. It will be convenient to refer throughout the remainder of the specification to the refined extract being mixed with the carrier, however it is to be understood that the refined extract may be further chemically and/or physically treated to derive the biologically active agents which are incorporated with the carrier to yield the composition for treatment of the conditions or achieving the effects described.

The direct introduction of the composition into body tissues or vessels may comprise intravenous, intramuscular or subcutaneous introduction into a treated body, although other methods of introduction may be used, e.g. intra-arterial, intraglandular, intraperitoneal injection.

The process for preparing a pharmac l gically ffective composition f r direct introduction into body tissu s r vessels

according to the present invention comprises the steps of extracting juice from Gramineae family plants, the juice being derived from green components of the plants, refining the juice so as to eliminate solids from the extracted juice to provide a liquid refined extract, the liquid refined extract being sterile, mixing the liquid refined extract in a pharmacologically acceptable liquid carrier for direct introduction into the body tissues or vessels.

Preferably the refining of the juice derived from the plants is carried out within two hours of the extraction of the juice from the plants. The refining operation to remove all solids preferably comprises a centrifuging operation followed by a fine filtration of a fraction separated after the centifuging.

Preferably the juice or the refined extract is stabilised within two hours of derivation from the plants, the stabilisation consisting of stabilisation by a process selected from: (1) the process of concentrating the juice or extract to provide a concentrated liquid, (2) the process of spray drying of the juice or refined extract, (3) the process of freeze drying of the juice or refined extract, and (4) the process of blending the juice or refined extract with a preserving agent. The fourth process of blending with a preserving agent is preferred.

It is believed that cereal plants are preferred, although other Gramineae family plants such as wild grasses for example may be used to yield the extract. Barley and wheat are suitable. The wheat may comprise Triticum vulgare or aestivum, T. durum, or T. compactum. A further possible cereal plant is triticale, a wheat-rye cross or hybrid. Corn, rye, rice, oats, maize, sorghum and millet may also be effective.

Preferably the juice is derived from the green leafy part of the plant, or at least principally from this part of the plant, although additional green parts such as stalk may be included. The leaves of the plant are preferably processed to yield the juice before the plant reaches flowering or seed production stage of development. That is, the plant is at its unjointed or immature development stage.

The juice extracti n is preferably carried out by squeezing, crushing and/ r grinding pr cesses, not by a cutting process and n t involving further cutting.

The juice is refined preferably by extracting water and water soluble only fractions of the juice, e.g. by centrifuging and filtration processes to remove all solids including bacteria or other micro-organisms. The processing of the juice may yield a fraction which includes fatty acids. This fraction may be used to produce or may be used as a component of the refined extract which is included in the carrier. Thus the water soluble only fraction and the fatty acid fraction may be both used if desired. Any components in the juice that are hydrophilic or hydrophobic but excluding solids may be effective or active ingredients and therefore may be included in the refined extract.

Although it is preferable to use the refined extract in the composition without concentration or further processing, it is possible for all the liquid content of the refined extract to be removed. For example, the refined extract may be dried, such as by spray drying to yield a powder for subsequent mixing with the carrier. The spray drying and all other processes including juice extraction and refining are preferably carried out at temperatures below about 50°C. Any heating to about 50°C or more is believed to denature proteins or other active ingredients and therefore efficacy can be reduced or destroyed by heating.

Other possible stabilisation processes for the juice include partial concentration of the derived juice or refined aqueous extract to provide a concentrated liquid, freeze drying of the derived juice or refined extract, and blending the derived juice or refined extract with a preserving agent forming an ingredient of the carrier.

Preferably the stabilisation or mixing with the carrier or both is carried out within a short time and preferably within two hours after juice extraction.

The carrier may be any pharmacologically acceptable liquid carrier and it is particularly expected that the refined extract will be used in an aqueous carrier solution. The carrier may be pure sterile water or may be, for example, a saline solution or other pharmacologically acceptable electrolyte or liquid.

If desired, a preservative agent may be included in or added to the refined extract and/or carrier or the composition. For example, ethanol in a concentration suitable for direct introduction into body tissues or vessels may b added as an anti-bacterial and pres rvative

agent, e.g. at 1% concentration in the refined extract but further substantially diluted in the carrier. Ascorbic acid or other anti-oxidant may be added in suitable concentration.

The ratio of the refined extract to the carrier may be anywhere within a large range of possible ratios. For example the ratio of liquid carrier to refined extract (and other additives if provided) may be anywhere between 1 to 50 and 50,000 to 1 (by weight). A range of 0.001 to 5% by weight of refined extract and preferably 0.1 to 2% may be usable.

The present invention also provides the use of a composition for the manufacture of a medicament for use in the treatment of pathological conditions by direct introduction into body tissues or vessels, the composition including a refined extract derived from Gramineae family plants, green components of the plants being processed to yield a juice and the juice being refined so as to eliminate all solid components and to provide the refined extract which comprises liquid fractions only from the juice, the refined extract being sterile, the composition further including a pharmacologically acceptable liquid carrier in which the refined extract is carried for direct introduction into the body tissues or vessels.

The pathological condition may comprise a tumour such as melanoma or sarcoma. The pathological condition may comprises a viral infection, including herpes. The envelope viruses are believed to be treatable with the compositions of the invention. Infections treatable are believed to include herpes, shingles, varicella, influenza and common cold, rubella, AIDS.

The composition may also be used for the manufacture of a medicament for use as an analgesic. Both local and general analgesic effects have been noted in use of the refined extract including use of topically applied extract and this analgesic effect is postulated in the case of direct introduction of the composition according to the present invention into body tissues or vessels.

The composition may furthermore be used for the manufacture of a medicament for use in the treatment of lesions, including wounds, skin cracking, ulcers, and bed sores, by direct introduction to body tissues or vessels. Reduction of scar tissue and particularly reduction of proud flesh formation in treatment of animal wounds has been associated with use of the composition of the invention.

The use of the composition for the manufacture f a medicament for use in the treatment of path logical conditions may be for the purpose of producing a medicament having a systemic effect in the body. Systemic effects have been noted following use of the refined extract including use by topical or local application. For example, skin conditions treated locally by topical application of the refined extract in a suitable carrier has achieved not only effective treatment of the local condition, but also improvements in the same or a similar skin condition at another part of the body not treated directly. It will be realised that the composition may be used for the manufacture of a medicament which is to be used for treatment of a local manifestation of the pathological condition, e.g. by direct introduction into the body tissues or vessels at the general site of the pathological condition.

The present invention also provides a method of treating a pathological condition in the body of a living animal by direct introduction of a pharmacologically effective composition according to the first aspect of the invention so as to facilitate dispension of the composition in the body. The method may comprise introducing the composition by means of a hypodermic needle, catheter or other means for directly introducing a liquid, e.g. intravenously, intramuscularly or subcutaneously.

For the treatment of a particular localised condition such as a skin or a subsurface infection, lesion or injury, the treatment may comprise direct introduction of the composition at the site of the condition being treated, e.g. so that the composition can be readily dispersed to the surrounding tissue by transport through the capillaries or other transport processes. For a more general body condition of a dispersed nature or for a condition which may be localised but in numerous locations, the substance may be introduced intravenously for general dispersion by the body circulatory system.

Of course, the pharmacologically effective composition of the present invention and the apparatus or medium used for introducing the composition into the body undergoing treatment must be sterile. As described above, the pharmacologically effective composition may be rendered and/or maintained substantially sterile by inclusion of an anti-microbial agent so as to kill or inhibit growth, reproduction or activity of contaminating organisms that may b present in the

plant juice or may be introduced during production of the comp sition. Of course, any such agent must be capable of safe introduction into the body. Alternatively, or in addition, the substance may be rendered or maintained substantially sterile by suitable handling and processing techniques such as irradiation e.g. with ultra-violet radiation, provided the effective ingredients are not destroyed by such processes.

The pharmacologically effective composition when introduced directly to tissues to be treated or directly introduced into the body, e.g. intravenously, intramuscularly or subcutaneously, enables the composition to be quickly and effectively brought to sub-surface tissues either by direct introduction or by being carried through the blood supply.

It is believed that the composition thus introduced into the body to be treated may be rapid in effective action on the treated tissues and the method of introduction can also lead to more effective action where sub-surface activity within deeper body tissues is desired.

The composition according to the present invention may be useful for treating pathological conditions including viral infections such as herpes 1, 2 and 3 (cold sores, genital herpes and herpes zoster or shingles). The composition may also be used for treatment of tumours as outlined in the example below. Analgesic effects have been noted and the composition may be used for the purpose of providing this analgesic effect. The composition has been observed to be associated with activation of blood circulation and dilation of blood vessels may be an effect. Activity of the composition as a dilator and constrictor of the baroreceptors has been postulated. Both systemic and local effects may be achieved and may be the intention of the treatment. The composition may be useful for treating and alleviating the symptoms associated with Karposis Sarcoma.

In the most general terms, the composition may be useful for treating responsive pathological conditions and for normalising abnormalities. The following pathological processes may be responsive to tr atment acc rding t the invention: genetic, inflammation (mechanical both physical and chemical), viral, bacterial, fungal, immun logical, neoplastic processes. Diseas s of

the following systems may be responsive: endocrine, candiovascular, respiratory, gastro-intestinal, haemat logical, urogenital, reproduction, dermatological, nutritional, metabolic disorders including inborn errors of metabolism, muscular disorders, bone metabolism, rheumatological disorders, and including local manifestations of systemic disease. Also the compostion may be useful as a preventative treatment for conditons referred to or in conjunction with other treatments to alleviate undesirable effects associated with such other treamtents, e.g. to alleviate ulcerations associated with radiotherapy and chemotherapy treatment of cancer patients.

The refined extract or a composition including biologically active agents from the refined extract may be ingested as a means of introduction to the body.

EXAMPLE

Refined extracts of barley grass and wheat grass were separately prepared according to the present invention. Doses were prepared at "half strength", "full strength", and "double strength", where "full strength" comprised the refined extract in sterile saline solution at a concentration of 10ml/kg. Toxicity tests were conducted by injecting mice intraperitoneally on days 1, 5 and 9. All mice given the full or double strength barley composition died on day 2. All mice given half strength barley dose and all mice given half strength, full strength and double strength doses of the wheat extract survived.

Tests were then carried out for the treatment of B16 tumour (a mice melanoma) using the following doses:

Barley extract doses at 1%, 25%, 50%, 75% and 100% of full strength;

Wheat extract doses at 1%, 25%, 50%, 100% and 200% of full strength dose.

The dilutions were made in sterile water. Injections were carried out intraperitoneally on days 1, 5 and 9.

Both compositions showed activity having a treated animal life span f 31% longer than untreated controls, i.e. %T/C=131, at a half strength dosage.

* * * *

It is to be understood that various alterations, modifications and/or additi ns may be made to the featur s f the possible and

preferred embodiment(s) of the invention as herein described without departing from the spirit and scope of the invention as defined in the appended claims.

CLAIMS

1. A pharmacol gically eff ctive composition for treatment of responsive pathological conditions by direct introduction into body tissues or vessels for treatment thereof or for treatment of proximate or remote tissues or for systemic effects, the composition including biologically active agents from a refined extract derived from cereal plants or other plants of the Gramineae family, green components of the plants being processed to yield a juice and the juice being refined so as to eliminate all solid components and to provide the refined extract which comprises liquid fractions only from the juice, the refined extract being sterile, the composition further including a pharmacologically acceptable liquid carrier in which the biologically active agents from the refined extract are carried for direct introduction into the body tissues or vessels.

2. A composition as claimed in Claim 1 characterised in that the refined extract comprises water and water soluble only fractions of the juice.

3. A composition as claimed in Claim 1 characterised in that the refined extract comprises a fraction of the juice which includes fatty acids.

4. A composition as claimed in Claim 3 characterised in that the refined extract also includes water and water soluble fractions of the juice.

5. A composition as claimed in any one of the preceding claims characterised in that the plants from which the juice is derived are selected from the group consisting of barley, wheat and triticale.

6. A composition as claimed in any one of the preceding claims characterised in that the plants are processed to yield the juice when the plants are at the unjointed stage of development.

7. A composition as claimed in any one of the preceding claims characterised in that the refined extract is itself mixed with the carrier to introduce the biologically active agents into the carrier.

8. The use of a composition for the manufacture of a medicament for use in the treatment of pathological conditions by direct introduction into body tissues or vessels, the composition including biologically active agents from a refined extract derived from Gramineae family plants, the green components f the plants being processed to yield a juice and the juice being refined so as to

eliminate all solid components and to provide the refined extract which comprises liquid fractions only from the juice, the refined extract being sterile, the composition further including a pharmacologically acceptable liquid carrier in which biologically active agents from the refined extract are carried for direct introduction into the body tissues or vessels.

9. The use of a composition for the manufacture of a medicament as claimed in Claim 8 characterised in that the pathological condition comprises a tumour.

10. The use of a composition for the manufacture of a medicament as claimed in Claim 8 characterised in that the pathological condition comprises a viral infection.

11. The use of a composition for the manufacture of a medicament as claimed in Claim 10 characterised in that the viral infection comprises herpes.

12. The use of a composition for the manufacture of a medicament for use as an analgesic by direct introduction into body tissues or vessels, the composition including biologically active agents from a refined extract derived from Gramineae family plants, green components of the plants being processed to yield a juice and the juice being refined so as to eliminate all solid components and to provide the refined extract which comprises liquid fractions only from the juice, the refined extract being sterile, the composition further including a pharmacologically acceptable liquid carrier in which the biologically active agents from the refined extract are carried for direct introduction into the body tissues or vessels.

13. The use of a composition for the manufacture of a medicament for use in the treatment of lesions by direct introduction into body tissues or vessels, the composition including biologically active agents from a refined extract derived from Gramineae family plants, green components of the plants being processed to yield a juice and the juice being refined so as to eliminate all solid components and to provide the refined extract which comprises liquid fractions only from the juice, the refined extract being sterile, the composition further including a pharmacologically acceptable liquid carrier in which the biologically active agents from the refined extract are carried for direct introduction into the body tissues or vessels.

14. The use of a composition for the manufacture of a medicament for

use in the treatment of pathological conditi ns by direct introduction into body tissues or vessels to promote dispersion of the composition for systemic effect, the composition including biologically active agents from a refined extract derived from Gramineae family plants, green components of the plants being processed to yield a juice and the juice being refined so as t eliminate all solid components and to provide the ref_ned extract which comprises liquid fractions only from the juice, the refined extract being sterile, the composition further including a pharmacologically acceptable liquid carrier in which biologically active agents from the refined extract are carried for direct introduction into the body tissues or vessels.

15. The use of a composition for the manufacture of a medicament for use in the treatment of pathological conditions by direct introduction of the composition into body tissues or vessels at the general site of the condition, the composition including biologically active agents from a refined extract derived from Gramineae family plants, green components of the plants being processed to yield a juice and the juice being refined so as to eliminate all solid components and to provide the refined extract which comprises liquid fractions only from the juice, the refined extract being sterile, the composition further including a pharmacologically acceptable liquid carrier in which the biologically active agents from the refined extract are carried for direct introduction into the body tissues or vessels.

16. A process for preparing a pharmacologically effective composition for direct introduction into body tissues or vessels, the process comprising the steps of extracting juice from Gramineae family plants, the juice being derived from green components of the plants, refining the juice so as to eliminate solids from the extracted juice to provide a liquid refined extract, the liquid refined extract being sterile, mixing biologically active agents from the liquid refined extract in a pharmacologically acceptable liquid carrier for direct introduction into the body tissues or vessels.

17. A process as claimed in Claim 16 characterised in that the refining f the juice derived from the plants is carried ut within two hours of the extraction of the juice from the cer al plants.

18. A process as claimed in Claim 16 or 17 characterised in that the

refining operation to remove all solids comprises a centrifuging operation followed by a fine filtration.

19. A method of treatment of a pathological condition in the body of a living animal including a human, other mammal or bird, comprising directly introducing a composition as claimed in any one of Claims 1 to 6 into tissues or vessels so as to facilitate dispersion of the composition within the body.

20. A method as claimed in Claim 19 characterised in that the direct introduction of a composition is carried out at the site of the pathological condition being treated.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/AU 91/00039

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl. A61K 35/78

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC	A61K 35/78

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category*	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X	AU,A, 81985/87 (599725) (DAVID RUDOV) 9 June 1988 (09.06.88)	1,2,5,6,7,10-16
X	GB,A, 1358052 (JAPAN NATURAL FOOD CO LTD) 26 June 1974 (26.06.74)	1,5,6,8,16
X	US,A, 3787591 (YOSHIHIDE HAGIWARA) 22 January 1974 (22.01.74)	1,5,6,7,8,16
X,P	US,A, 4943433 (DAVID RUDOV) 24 July 1990 (24.07.90)	5-16
X	Patent Abstracts of Japan, C-25, page 156, JP,A, 55-87725 (YOSHIHIDE HAGIWARA) 2 July 1980 (02.07.80)	1,7,8,16,18
X	Patent Abstracts of Japan, C-139, page 84, JP,A, 57-146715 (NIHON YAKUHIN KAIHATSU K.K.) 10 September 1982 (10.09.82)	1,7,8,12,14,15,16, 18

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
	17 MAY 1991
International Searching Authority	Signature of Authorized Officer
Australian Patent Office	JOHN C HANSON

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.[] Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2.[] Claim numbers ..., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.[] Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1. [] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[] The additional search fees were accompanied by applicant's protest.

[] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 91/00039

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Members		
US 3787591	US 3787591		
US 4943433	AU 81985/87	AU 599725	DK 6335/87
	EP 881012	DK 6335/87	EP 279984
	IL 84668	JP 1502820	NZ 222758
	US 4943433	WO 8804176	ZA 8709053
AU 81985	AU 81985/87	AU 599725	DK 6335/87
	EP 279984	IL 84668	JP 1502820
	NZ 222758	US 4943433	WO 8804176
	ZA 8709053		
GB 1358052	GB 1358052		

END OF ANNEX